

NERVOUS SYSTEM AND INTERNAL SECRETION

LEON ASHER

University of Berne, Switzerland

Internal secretion has become a problem of widespread interest since an overwhelming array of facts has been found showing that hormones are the fundamental and indispensable instruments by which the functions of the animal body are regulated and coordinated. To a great extent life as a whole is integrated by hormones. Former discoveries in this field led, and with reason, to a growing belief that, as Sterling expressed it, chemical regulation is not only the older but also the more widespread and fundamental form of coordinatory mechanism.

This latter view eventually led to a lesser estimation of the nervous system, to which, up to that time, had been ascribed the preponderant influence as regulator of functions. Too, another factor has contributed for quite a time to studying internal secretion without regard to the central nervous system, namely, that hormones appear to act whether a tissue is innervated or not. Internal secretion apparently continues even after all connections between the nervous system and glands of internal secretion have been severed.

On the other hand, the question whether hormones had any influence on the nervous system has not received sufficient attention. This neglect was for a time justified, as first of all the better defined reactions of peripheral structures and functions had to be determined, especially as the results could be expressed in more or less quantitative terms. Most valuable and trustworthy information on the activity of hormones has been obtained in this manner.

Nevertheless, earlier observations had suggested a striking influence, especially of one gland of internal secretion on the central nervous system. From the very beginning of modern study of the thyroid gland it had been recognized that young individuals with varying deficiencies of the thyroid gland developed cretinism, characterized, among other features, by inferior intelligence and mental activity. Naturally this was taken as proof that the thyroid has an influence on the central nervous system. However, the question remains open whether mental disablement is not a secondary phenomenon due to the arrested

development of the cells of the cortex of the brain. Also in young animals symptoms of mental inactivity become apparent following thyroidectomy.

To arrive at a more intimate knowledge of the relation between glands with internal secretion and the activity of the central nervous system investigation of the thyroid gland appears particularly significant, since it is especially adapted to study and has, in addition, an outstanding position as regards its influence on the central nervous system. Notwithstanding this situation we had to work out methods for quantitatively estimating this influence. It was necessary to state in exact units the intensity of the stimulus acting on the central nervous system as well as the intensity of a well-defined response. The postulated demands were fulfilled by various methods developed for our purposes in the Physiological Institute of the University of Berne.

I will begin with the reaction of the respiratory centre in the medulla. This is stimulated by CO_2 . The strength of this stimulus can be quantitated by having an animal breathe air of either 20 or 40 mm. CO_2 tension. The response is then exactly measured by observing the amount of air breathed in one minute through a gasometer. When the increase of the minute volume of respiration of the normal animal inspiring these air mixtures is known, we inject the hormone of the thyroid gland, best in the form of thyroxin. The usual augmentation of respiration is increased but what is especially striking is the fact that three and a half hours after injection of thyroxin, this augmentation is already marked. It is the earliest response which thyroxin evokes, while the first metabolic effects do not appear before 24 hours. This time relation is significant as it shows that the primary effect of the internal secretion of the thyroid is on the central nervous system. After thyroidectomy the reaction is reversed and the excitability of the respiratory centre is much lower. The opposite changes in excitability after injection of thyroxin and after thyroidectomy are also noted if one records the frequency of respiration of animals subjected to raised environmental temperature; the increase, compared with the normal animal, is greater after thyroxin, and smaller after extirpation of the thyroid.

It is of interest that extirpation of the spleen acts in the same direction on the respiratory centre as an increase in the activity of thyroid gland. This suggests that as long as the

spleen is in the body, it exerts an inhibitory action on the respiratory centre and therefore the withdrawing of this influence is equivalent to an augmentation of thyroid activity on the nervous system. This deduction is supported by the fact that injection of a purified spleen extract produces a relative inhibition. The antagonistic balancing influence of thyroid and spleen is not restricted, by the way, to the nervous system; it also appears in the regulation of peripheral functions.

The influence of thyroid secretion on the higher levels of central nervous system activity was studied by quantitative investigations of the reflex response to stimulations with light or sound. We subject, for instance, the eye of a rabbit to light of which the intensity, distance from the eye and duration are exactly measured. After the threshold value for contraction of the pupil of the given normal animal has been determined, thyroxin is injected. If this is repeated two or three times, the threshold value for eliciting the reflex is found to be greatly decreased; consequently, the sensitivity of this mechanism is increased. Guinea pigs react precisely to a high pitched sound with a rapid movement of the ear. This reflex is an interesting instance contrary to a current notion that reflex activity is necessarily subject to fatigue. In reality this reflex appears to be in a high degree indefatigable. For, if the stimulus is repeated every second, the animal will respond without fail for an hour or more with the rapid jerk of its ears. The intensity of the stimulus is easily measured by the pressure which is necessary to drive the air through a Galton pipe for attaining the threshold intensity of sound. The distance of the pipe from the animal is kept constant. Again after increasing experimentally the thyroid secretion, the animal becomes far more sensitive to sound while thyroidectomy greatly depresses its sensitivity.

Even those parts of the brain to which we ascribe the highest functions, namely, the cortex of the forebrain, can experimentally be recognized as affected by the thyroid hormone. Narcosis by ether, as used in surgery to make operations painless for the patient, is mainly a temporary inhibition of the highest centers of the cerebral cortex; in human beings the seat of consciousness. If the thyroid hormone is capable of sensitizing the cortex, we should expect in states of hyper- and hypothyroidism a different reaction towards narcotics than in the normal state. This expectation is readily verified under the condition that a narcotic is administered by a method that allows a quantitative

estimation of the amount of narcotic substance necessary to produce narcosis under controlled conditions of application and time. The method we employed was to drive ether mixed with known amounts of air under constant pressure through stop-cocks of graded dimensions and measuring the amount of ether used as soon as narcosis was attained. The latter value was remarkably constant for a given individual. Animals under the influence of increased thyroid hormone were far more resistant to narcosis than in the normal state. We should be justified to draw the conclusion that thyroid internal secretion raises the vitality of the higher parts of the brain, a conclusion, of course, not new to us, as intellectual deficiency is known to us from cretinism based on lack of thyroid activity.

At the present state of our knowledge the thyroid is outstanding in demonstrating the relation between nervous system and internal secretion. Less is known regarding the other glands of internal secretion, with the exception of the gonads. Loss of the latter does not alone extinguish the sexual functions, but also to a certain extent depresses the vivacity of certain of the nervous activities. What has frequently been viewed as a kind of rejuvenation is more probably a temporary reactivation of the nervous system by the introduction of appropriate sexual hormones. Perhaps if we are able to develop more refined methods to test the activity of the brain, we shall know more about the influence of the hypophysis and the adrenal glands on nervous activity, an influence which we are warranted to presume.

Notwithstanding the fact that glands with internal secretion are autonomic, a regulatory influence of the nervous system on their secretion must be postulated, as anatomy shows them to be richly innervated. Experimental investigation has given decisive proof of a regulatory nervous control of internal secretion. The evidence for the adrenal gland, insofar as adrenalin, the hormone of the medullary substance, is concerned, is clear cut. Stimulation of the splanchnic nerves, whether experimentally through induction currents or naturally by various reflexes, causes an output of adrenalin into the blood. Whenever through muscle work, or fear, rage and other emotions, greater demands are imposed on the organism, the central nervous system leads by natural impulses to a secretion of adrenalin. In this way, as Cannon ably has put it, the adrenal gland becomes one of the helpmates of the organism to overcome the stress and strain of life.

The frequency of diabetes has directed popular attention to the pancreas, which, by way of its islet cells produces insulin, the powerful regulator of carbohydrate metabolism. Previous to the discovery of insulin, my collaborator, Dr. de Corral from Madrid, showed that stimulation of the vagus nerve caused the level of blood sugar to become lowered, which is precisely, since we now know insulin, the reaction to increased secretion of this hormone. By employing more modern methods Zunz in Brussels has corroborated in a most convincing manner the nervous control of the regulation of carbohydrate metabolism by insulin.

The question of the nervous regulation of thyroid secretion was for a long time beset with peculiar difficulties. But they have been overcome since we have learned to use well-defined reactions of the thyroid internal secretion which take into consideration the time in which these reactions gradually develop. Absorption of fluid from the subcutaneous tissue of a lower extremity takes a certain time and it is of approximately the same duration whether the animal is in a cold or warm environment. This becomes different when the thyroid is denervated. The absorption time is then longer and an appreciable difference between cold and warmth appears. Evidently the regulation of absorption has become impaired. That this is exclusively due to the denervation of the thyroid is further demonstrated by the fact that the said difference is accentuated by thyroidectomy. Through the more refined method of thermoelectrical measurement of the temperature of the liver, we were able to show that after denervation of the thyroid, thermo-regulation in the liver as a response to cooling worked less efficiently and again that thyroidectomy magnified this inefficiency.

By way of the sympathetic nerves the intensity of the thyroid secretion is adjusted to the needs of the organism. I have before drawn attention to the influence of the thyroid secretion on the central nervous system. The influence just shown, in the reverse direction from the central nervous system on the thyroid, allows the suggestive inference, that central nervous system and thyroid are functionally linked together in shape of a circuit and that both are reciprocally interdependent. In consequence of this, when impulses from the nervous system stimulate thyroid secretion, the latter will lead to an increased activity of the nervous system and we shall see exactly as in the case of the heart, excitations incessantly going on in both direc-

tions, eventually leading to the diseased state of hyperthyroidism and nervous instability, until medical aid breaks the vicious circle.

It is appropriate to close my talk with the hypophysis, the remarkable gland at the base of the brain, unique in its dominating position over most of the glands with internal secretion and a ruler besides of important bodily functions of a general character. But even this powerful gland is subject to nervous regulation, emanating from pathways in the hypothalamus as recent fine work from American neurologists has demonstrated.

I thank the distinguished audience for the kind patience with which it has followed my lecture. It would be gratifying to have been in a little way successful in drawing a picture of the building up of life's regulation by nervous and hormonal control. Life shines out as a unity and as such is lavish in employment of means to its ends.
